Remarks

In view of the above amendments and the following remarks, reconsideration of the grounds of rejection set forth in the outstanding office action is respectfully requested.

Claims 1 and 3–5 have been amended, and claim 32 has been cancelled without prejudice. No new matter has been added by way of these amendments.

This submission is accompanied by a petition for one-month extension of time, an Information Disclosure Statement ("IDS") listing five references (two PCT references cited in an examination report for a corresponding Japanese application, along with two U.S. patent documents as English language translations of these PCT references), and a Second Declaration of Henry Nicolas Jabbour under 37 C.F.R. § 1.132 ("Second Jabbour Declaration"). The IDS is being filed pursuant to 37 C.F.R. § 1.98(d).

The rejection of claims 1, 3–5, 9, 12–13, and 32 under 35 U.S.C. § 112 (first para.) for failure to comply with the enablement requirement is respectfully traversed.

The United States Patent and Trademark Office ("PTO") asserts at page 4 of the office action that the specification and applicants' arguments, including those based on the Declaration of Henry Nicolas Jabbour under 37 C.F.R. 1.132 ("First Jabbour Declaration"), submitted February 26, 2009, "only prove that the FP receptor might play a role in the disease of the uterus claimed by the applicant (uterine cancer, fibroids and endometriosis), and definitively is an invitation for further research in this area. However, these arguments do not demonstrate that an FP receptor antagonist could treat any of these diseases. There is no *in-vitro* or *in-vivo* data and/or proof of mechanism in the instant application and in the literature of any kind to suggest that an FP antagonist might be useful in the treatment of uterine cancer, fibrosis and endometriosis" (emphasis in original). Applicants respectfully disagree.

As set forth in MPEP § 2164.04, a specification disclosure that contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and back up assertions of its own with

acceptable evidence or reasoning which is inconsistent with the contested statement (MPEP § 2164.04 (quoting *In re Marzocchi*, 439 F.2d 220, 224 (CCPA 1971))). Applicants submit that the PTO has failed to meet its burden in making the enablement rejection.

The specification of the present application demonstrates the localization of FP receptor expression in proliferating epithelial cells of human endometrium (*see* specification at page 31, lines 9–12 and Figure 2A). A significant increase in FP receptor expression was observed in mid- and late-proliferative uterine adenocarcinoma tissue compared to non-cancerous tissue (*id.* at page 31, lines 19–23 and Figure 2B). FP receptor function in endometrial adenocarcinoma cells was confirmed by mobilization of inositol phosphate (*id.* page 32, lines 1–7 and Figure 3) and phosphorylation of ERK (*id.* page 32, lines 8–11 and Figure 4). Additionally, endometrial adenocarcinoma cell proliferation increased in a $PFG_{2\alpha}$ (the FP receptor ligand) concentration dependent manner (*id.* page 32, lines 12–14, and Figure 5).

Based on this data presented in the specification, one of skill in the art would have no reason to doubt that FP receptor expression and function plays a role in pathological conditions of the uterus that are associated with abnormal myometrium and endometrium cell growth and proliferation such as, uterine cancer, fibroids, and endometriosis. Accordingly, one of skill in the art would have no reason to doubt that FP receptor antagonism would be useful in treating uterine cancer, fibroids, and endometriosis as recited in amended claim 1.

The PTO acknowledges that the specification and previously submitted arguments prove that the FP receptor might play a role in uterine disease as claimed (office action at page 4), but fails to provide evidence or reasoning as to why one of skill in the art would doubt that FP receptor antagonism is useful in treating uterine cancer, fibroids, and endometriosis.

As discussed below, and for the reasons addressed in the accompanying Second Jabbour Declaration, subsequent work performed under Dr. Jabbour's supervision further supports the enablement of FP receptor antagonism for treating uterine cancer, fibroids, and endometriosis as described in the patent application.

In the First Jabbour Declaration, Dr. Jabbour discussed the significance of data presented in Sales et al., "A Novel Angiogenic Role for Prostaglandin F2α-FP Receptor Interaction in Human Endometrial Adenocarcinomas," (2005) *Cancer Res*. 65, 7707-7716 ("Sales"). The work presented in Sales shows that elevated FP receptor and VEGF expression co-localized in glandular and epithelial cells lining the blood vessels in

endometrial (uterine) adenocarcinomas (Second Jabbour Declaration at ¶ 4). Furthermore, it shows that PGF2α (the natural ligand of the FP receptor) can cause rapid transphosphorylation and activation of the EGF receptor, activation of MEK signaling via the FP receptor resulting in an increase in VEGF promoter activity, and expression of VEGF mRNA and secretion of VEGF protein, all of which are consistent with a role for the FP receptor in stimulating blood vessel formation (angiogenesis) in endometrial (uterine) cancer (*id.*).

Sales investigates the effect of a specific FP receptor antagonist, namely AL8810, in a way that is directly relevant to establishing that FP receptor antagonists have relevant activities for the treatment of uterine cancer, endometriosis and fibroids (Second Jabbour Declaration at ¶ 5) . In particular, it investigates the effect of the FP receptor antagonist on the PGF2α signaling to VEGF in endometrial adenocarcinoma using endometrial adenocarcinoma (Ishikawa) cells and using endometrial adenocarcinoma tissue explants (*id.*).

Sales discloses that the effects of PGF2α on the FP receptor could be abolished by treatment of cells with a specific FP receptor antagonist, AL8810 (Second Jabbour Declaration at ¶ 6). This can be seen from page 7711, column 2, and from Figure 4b, lane 3 of Sales, which notes that the activation of ERK1/2 was abolished by co-treatment with AL8810 (*i.e.*, treatment with PGF2α and AL8810) (*id.*). Figures 5A and 5B of Sales further show AL8810 treatment prevents PGF2α-FP mediated increase in VEGF mRNA expression and protein secretion in Ishikawa cells (*id.*).

Furthermore, similar effects were found when endometrial adenocarcinoma explants were treated with AL8810 (Second Jabbour Declaration at ¶ 7). This data shows that AL8810 abolishes PGF2α mediated increase in tyrosine phosphorylation of EGFR (*id.*). EGFR is known to be involved in many cancers, and these results show that the FP receptor induces the activity of EGFR in endometrial cancer, and more importantly the results show that an antagonist of the FP receptor inhibits the activity of EGFR induced by PGF2α (*id.*). Hence, the FP receptor antagonist inhibits not only the FP receptor, but also indirectly the activity of another receptor (EGFR) with renowned roles in cancer (*id.*). Moreover, Figure 6b of Sales demonstrates that AL8810 treatment prevents PGF2α-FP mediated increase in VEGF mRNA expression in endometrial adenocarcinoma explants (*id.*).

In addition to the data described in Sales, Dr. Jabbour has carried out additional studies investigating the role of FP receptors in endometrial (uterine) carcinoma

which further support the enablement of the claimed invention (Second Jabbour Declaration at ¶ 8).

The results of one such study are described in Keightley et al., "F-Prostaglandin Receptor Regulates Endothelial Cell Function via Fibroblast Growth Factor-2" ("Keightley") which has been submitted for publication in the journal *Biochim. Biophys. Acta* (Second Jabbour Declaration at ¶ 9). This manuscript describes work carried out under the supervision of Dr. Jabbour and shows that F-prostaglandin receptor (the FP receptor) regulates endothelial cell function via Fibroblast Growth Factor-2 (FGF-2) (*id.*). Angiogenesis (the formation of new blood vessels) has an important part to play in endometrial (uterine) carcinogenesis and this requires the processes of endothelial cell differentiation (or network formation) and proliferation, both of which are therefore targets for therapeutic intervention (*id.*).

Particularly relevant is the first full paragraph on page 16 of Keightley which describes the effect of PGF2α-FP receptor interaction in endothelial network formation (Second Jabbour Declaration at ¶ 10). It can be seen that the FP receptor antagonist AL8810 prevented an increase in endothelial network formation, which is necessary for angiogenesis, again clearly supporting the use of FP receptor antagonists for treating endometrial (uterine) carcinoma, which requires angiogenesis (*id.*).

Wallace et al, "Prostaglandin F2α-F-Prostanoid Receptor Signaling Promotes Neutrophil Chemotaxis via Chemokine (C-X-C Motif) Ligand 1 in Endometrial Adenocarcinoma," (2009) *Cancer Res.* 69, 5726-5733 ("Wallace") also describes work carried out under Dr. Jabbour supervision (Second Jabbour Declaration at ¶ 11). Wallace shows that the FP receptor upregulates expression of CXCL1, a chemokine involved in the inflammatory pathways in tumours, and this is inhibited by treatment with the FP receptor antagonist AL8810 (*id.*). Wallace goes on to show that the CXCL1 upregulation by FP receptor results in increased attraction of neutrophils into the uterine cancer microenvironment which is believed to enhance angiogenesis and promote metastasis (*id.*). Hence, antagonism of the FP receptor, which blocks the expression of CXCL1, will reduce inflammatory pathways in uterine cancer and suppress the influx of neutrophils (*id.*).

Consistent with the description in the present application (see in particular the conclusion to Example 1 on page 34, lines 8 to 24), the results in Sales, Keightley, and Wallace confirm that an FP receptor antagonist can play a direct role in treating a pathological condition of the uterus, such as uterine carcinoma (Second Jabbour Declaration

at ¶ 12). AL8810 is one of the FP receptor antagonists specifically exemplified in the patent application at page 9, lines 1-7 (*id.*).

The data submitted as Annex 4 of the First Jabbour Declaration provides additional data showing that FP receptor expression is consistently higher in the endometrium of women with fibroids, during all phases of the menstrual cycle, than those without fibroids (Second Jabbour Declaration at ¶ 13).

In this study, which was conducted in Dr. Jabbour's laboratory under his supervision, endometrium was collected from women with fibroids and those without, RNA was extracted from these tissues and then the level of expression of the FP receptor from the two groups of women was assessed by a technique known as reverse transcriptase polymerase chain reaction (this technique allows one to make direct comparisons of the levels of expression of the receptor in different women) (Second Jabbour Declaration at ¶ 14). In the endometrium of women with fibroids, the level of expression of the FP receptor was consistently higher (*id.*).

Taking into account his knowledge of the mechanism of action of the FP receptor and its role in exacerbating vascular function, Dr. Jabbour expected that antagonizing the action and signaling of this elevated FP receptor in the endometrium of women with fibroids would be an effective therapeutic intervention strategy that may limit the blood loss that is associated with this pathology (Second Jabbour Declaration at ¶ 15). For the reasons discussed above, this gives further credibility that FP receptor antagonists are useful in treating pathological conditions of the uterus, including fibroids (*id.*).

Accordingly, Dr. Jabbour maintains his conclusion that the data presented in the present application and obtained subsequent to the filing date confirm that several uterine pathological conditions, including endometriosis, uterine carcinoma, and fibroids, all involve enhanced FP receptor expression; and, consistent with the description in the application for treating such uterine pathological conditions, treatment of uterine carcinoma explants with an FP receptor antagonist was shown to be effective in preventing FP receptor mediated expression of pro-angiogenic factors like VEGF and in inhibiting endothelial network formation, which are essential features of angiogenesis in uterine carcinoma (Second Jabbour Declaration at ¶ 16).

The results therefore confirm the efficacy of treating pathological conditions of the uterus using FP receptor antagonists. Given the demonstrated efficacy of treating uterine carcinoma explants with an FP receptor antagonist, persons of skill in the art would

fully appreciate that a female individual having a pathological condition of the uterus, such as uterine carcinoma, endometriosis, uterine fibroids, or any other pathological conditions of the uterus that are associated with abnormal growth of the myometrium or endometrium, can be effectively treated for the condition by administering to the affected individual an FP receptor antagonist (Second Jabbour Declaration at ¶ 17).

The PTO asserts that "[a]pplicant did not provide a single cell assay that shows that any FP receptor antagonist could prevent or ameliorate the proliferation of a cancerigenous [sic] cell" (office action at page 6). However, as acknowledged by the PTO, "[c]*ancer is a very complex disease that involves several mechanisms*". Accordingly, direct prevention of the proliferation of cancerous cells is not a requirement of an anti-cancer agent. The data presented in the First and Second Jabbour Declarations shows that FP receptor antagonism inhibits processes that are essential for angiogenesis in uterine carcinoma. The inhibition of angiogenesis is a well accepted target for the treatment of cancer and other conditions associated with abnormal growth and cellular proliferation.

In view of the compelling evidence demonstrating the involvement of FP receptor in endometrial cancer, the direct and relevant effects of FP receptor antagonism on events involved in cancer progression (network formation and angiogenesis), and the failure of the PTO to present any evidence to the contrary, one of skill in the art would have no reason to doubt that FP receptor antagonists are useful in treating uterine adenocarcinoma cancer, endometriosis, and fibroids as claimed. Accordingly, the rejection of claims 1, 3–5, 9, 12–13 and 32 under 35 U.S.C. § 112 (first para.) for failure to comply with the enablement requirement is improper and should be withdrawn.

In view of all of the foregoing, applicants submit that this application is in condition for allowance and such allowance is respectfully requested.

Respectfully submitted,

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